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The Personalized Medicine Approaches in The Treatment of Corona Virus Disease2019- (COVID19-): A Review

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Abstract:
Personalized medicine is the clinical treatment of diseases that is tailored to the physiologic, molecular genetics and lifestyle characteristics of the patient.
Personalized medicine can be considered as a new approach to face diseases and develop traditional methods for their diagnosis and treatment. This novel field of medicine has the potential of changing identification and management of health problems strategies. Corona virus disease 2019 (COVID-19) is an infectious disease that affects the lungs of patients. This novel outbreak was first reported on 31 December 2019 in Wuhan, the capital of Hubei province of China, and it had many effects on people's lives all over the world in various economic, social and health fields until now. Since the start of the pandemic Covid-19, the World Health Organization (WHO) has expressed concern about the public health emergency. Although the disease has mild symptoms and similar to a common cold in most people, in some cases it can lead to pneumonia, acute respiratory distress syndrome, multi-organ dysfunction, and even death. Therefore, due to the different effects of this disease in individuals and even families, the role of personalized medicine becomes more significant and sensitive. Considering the rapid spread and global crisis of Covid-19, recent research has focused more on the control and treatment of the virus. The main goal of this paper is the investigation of different effects of the virus on patients and study of the personalized medicine roles in the control and treatment of the disease.

INTRODUCTION

Corona virus 2: Pathogenicity, Transmission and Spread

After a severe acute respiratory syndrome disease broke out in Wuhan, China in December 2019 and it affected the whole world; on 7 January 2020 the virus was identified as a corona virus with more than 95% similarity to bat corona virus and more than 70% similarity to SARS-CoV. The body's areas affected by COVID-19 were six times higher than those affected by severe acute respiratory syndrome (SARS) (1).

Corona viruses are classified into four main genera: α-CoV, ß-CoV, γ-CoV and δ-CoV. The α-CoV and ß-CoV are capable of infecting mammals, while γ-CoV and δ-CoV tend to infect birds(2). Already, six corona viruses were known to cause infection in humans. Among them, α-CoV strains (HCoV-229E and HCoV-NL63) and ß-CoV strains (HCoV-HKU1 and HCoVOC43) have low infectivity and cause only mild respiratory infections similar to common colds. The two most well-known ß-CoVs; SARS-CoV and MERS-CoV; can cause severe and possibly life-threatening respiratory symptoms. Based on available evidence from genome sequencing and evolutionary analysis, bats have been proposed as the reservoir and natural origin of SARS-CoV-2. Bats may transmit the virus to humans through unknown intermediate hosts (3-5). Corona virus can easily move between species. In this way, Lu et al found that an important factor in corona transmission is the spike glycoprotein S1, which tightly binds to the angiotensin-converting enzyme2 (ACE2) receptor and enters the host cell. The basis of the corona virus pathway depends on ACE2 and protease/serine subfamily 2 (TMPRSS2) cleavages, particularly in the airways and cavities (6).In an experiment by Yang et al., mice over expressing human ACE developed more severe disease when infected with SARS-COV (7). ACE2 is found in various tissues

and organs such as kidneys, heart, intestines and blood vessels (8-15).

Also, ACE2 is expressed in type 2 epithelial cells, which play a key role in pulmonary gas exchange by producing surfactant. Therefore, any damage to these structures causes a disorder in the lungs (16).SARS-COV down regulates ACE2 expression, thereby causing damage to the lungs. Hence, ACE2 plays a dual role in both SARS-COV entry into cells and lung protection against injury (17-19).

The rate of human-to-human transmission of the new corona virus is significantly high, which leads to a wide expansion of clinical observations in infected patients (20). Although the absolute number of deaths related to COVID-19 was high, it appears that SARS-CoV-2 has a lower mortality rate than SARS-CoV or Middle East respiratory syndrome corona virus (MERS) (21). There is a lot of evidence that many cases of COVID-19 are asymptomatic, but they can transmit the virus to others (22). Detection of asymptomatic infections is essential for the prevention and timely control of COVID-19 worldwide (23). The spread of COVID-19 has been rapid. Due to the high binding affinity of SARS-CoV-2 to human angiotensin-converting enzyme 2 (ACE2), the main cellular receptor of the corona virus, its transmissibility is much higher than that of SARS (24). In the early stages of infection, the effective number of replications of SARS-CoV-2 was estimated to be 2.9, compared to 1.77 for SARS virus. Direct transmissions, airborne and contact are the three main transmission routes of SARS-CoV-2 (25). Many patients with COVID-19 have flu-like symptoms, including cough, fever, fatigue, anorexia, sputum production, and shortness of breath (26). Most people experience only mild symptoms, However, COVID-19 can also cause severe acute respiratory syndrome (ARDS), which often leads to intensive care unit (ICU) admission and death (27). Respiratory failure caused by ARDS is the main cause of death; but due to viral invasion of organs with high ACE2 expressing cells, patients with non-respiratory symptoms such as kidney failure or damage to the function of male gonads have also been reported in some cases (28,29). Based on these reports, the duration of the infection period of COVID-19 appears to consist of three basic phases: the first incubation period is largely asymptomatic, followed by the onset of symptoms in the second phase, which is nonspecific and non severe, with a subset of Patients progressing to the third stage with severe lung disease, it is often associated with extra pulmonary organs dysfunction (30-33).

Evidence-based medicine, personalized medicine and covid-19

The prediction of drug response of patients to make sure about patient safety and better drug effectiveness introduced “evidence-based medicine” in the early of 1950s and this was followed by the creation of personalized medicine field. Combination of modern medicine and molecular biology for treatment of patients separately based on individual characteristics in order to improve the treatment efficacy and better responses of patients to drug and reduce the drugs side effect is the main goal of personalized medicine. The evolution of genotyping techniques, biochips and single nucleotide polymorphisms (SNPs) in the past years has allowed researchers to find genetic differences between people in certain regions of genes and to perform treatment based on individual characteristics (34).

Researchers have proven that variations of human genome increase the risk of diseases such as cancer, cardiovascular and neurodegenerative diseases, diabetes and infectious diseases. However, environmental and lifestyle factors also have a great impact on disease progression, so personalized medicine should consider genome variations along with environmental factors in order to provide more efficient solutions for treatment (35).

Evidence-based medicine requires patients who share enough of a common condition that their responses are generalizable to a clinical practice. This evidence-based medicine seems to be in contrast to personalized medicine, which emphasizes aspects of each patient and thus makes them unique and personal (36).

Despite all the worldwide achievement and efforts for diagnosis and treatment of Covid-19, a definitive solution for the treatment of this disease has not yet been provided by modern medicine. Patients with COVID-19 not only are not all the same, they can also differ profoundly in terms of severity and pathophysiology. The main factor of drug efficacy and toxicity in the covid-19 patients is the genetic background of them (37). recent studies showed that two ACE2 alleles (i.e., rs73635825 and rs143936283) probably reduced viral attachment and increase resistance to infection (38). Moreover, researchers demonstrated that chromosome 3p21.31 (rs11385942) and chromosome 9q34.2 (rs657152) related to the ABO blood group involved in

COVID-19 patients with respiratory failure (38). Other genomic variations associated with COVID-19 disease severity in chromosomes 1 (1q22.1), 2 (2p21.1), 3 (3p21.1–3), 6 (6p21.1), 8 (8q24.13), 9 (9q34.1–2), 12 (12q24.1–2), 17 (17q21.3), 19 (19p13.1–3) and 21 (21q21–q22 have been reported (39, 40). However, it is still difficult to ensure about this findings because the limitation of testing methods and study population.

Along with the pathophysiology of the infection caused by COVID-19, the immune responses in these patients can be categorized into phases. Phase I, the initial innate immune response that is critical for the host to provide an antiviral defense in the lung, and

the subsequent phase that leads to intense local and systemic immunity are responses that contribute to morbidity and mortality (36). The heterogeneity of COVID-19 requires us to apply the principles of both evidence-based medicine and personalized medicine.

Due to the limitations of experimental methods for identification of covid-19 pathogenicity, various drugs such as IFN-a, lopinavir/ritonavir, chloroquine phosphate (or hydroxychloroquine), azithromycin, ribavirin, arbidol and remdesevir are recommended for patients at different stages of the disease. According to personalized medicine principles, the effectiveness of these drugs will definitely be different in diverse regions of the world. Unfortunately, there is no global organization to monitor the impact of environmental and regional factors, weather, genetic factors and lifestyle on the effectiveness of covid-19 drugs (34).

Personalized medicine approaches to COVID-19, including the pathogenesis of COVID-19 and the development and use of diagnostic kits, have played a key role in countries' response to the outbreak (32, 33). The medicine approaches are moving from traditional medicine to personalized medicine. As the law develops and improves, we are more able to employ the principles of personalized medicine. Personalized medicine strategies in other infectious diseases also show unique advantages. Considering these issues, we believe that with rapid development of molecular diagnosis technology and increasing awareness of the cost-effectiveness of personalized medicine, the applications of personalized medicine in the field of infectious diseases will lead to better management and treatment of them (41, 42).

Researchers have discovered hundreds of genes with mutations that contribute to human disease, identified genetic variation in patients' responses to dozens of treatments, and are working to target the molecular causes of some diseases. In addition, scientists are developing the use of diagnostic tests based on genetics or other molecular mechanisms to better predict patients' response to targeted therapy. Currently, personalized medicine is focused on the best ways to develop new treatments and optimize prescribing by guiding patients to the right drug, the right dose, at the right time. Achieving these goals includes scientific challenges, such as which genetic markers have the most clinical significance, limiting the off-target effects of gene-based therapies, and conducting clinical studies to identify genetic variation that is associated with drug response. As genetic researchers generate vast amounts of new information, the FDA (Food and Drug Administration) is developing regulatory science standards and the evidence required for the use of genetic information in drug and device development and clinical decision-making (43). On the other hand, genetic tests are not perfect and do not fully predict outcomes, partly because of most gene mutations. So it is necessary for physicians to understand the specificity and sensitivity of new diagnoses. It is also anticipated that some previously rejected drugs will be found to be safe and effective and will be approved for subgroups of patients with specific genetic markers (44).

CONCLUSION

Personalized medicine means escaping the "one medicine fits all" approach to medicine focusing on the individual characteristics of each patient. The transition from the old approach, traditional medicine, to the new approach, personalized medicine, requires the amendment of existing laws. Following the spread of the pandemic virus of COVID-19 and the infection caused by this virus and the different immune responses of people to this virus and the drugs prescribed for it, the role of personalized medicine became more prominent. In order to apply personalized medicine methods in COVID-19 healthcare, we must adhere to ethical and practical principles to ensure its safety and effectiveness.

At the same time, personalized medicine may be associated with challenges from different aspects. One of these challenges is people's awareness about personalized medicine. Patients should be empowered to participate in the decision-making process. Another challenge is funding for personalized medical research and diagnostics. Therefore, personalized medicine is very suitable for dealing with infectious diseases, including COVID-19. This method can be used to evaluate the pharmacogenetic characteristics of patients to help with treatment decisions and reduce the risk of side effects. Due to recent advances, personalized medicine can be more convenient, less expensive and more efficient in treatment.

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